RESEARCH ON MICROBIAL BIOFILMS

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National Institute of Dental Research
National Institute of Allergy and Infectious Diseases
National Institute on Deafness and Other Communication Disorders
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of General Medical Sciences
National Heart, Lung, and Blood Institute
National Institute of Diabetes and Digestive and Kidney Diseases
Office of Research on Women's Health

PURPOSE

The National Institute of Dental Research (NIDR), National Institute of Allergy and Infectious Diseases (NIAID), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of General Medical Sciences (NIGMS), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and Office of Research on Women's Health (ORWH) invite research grant applications to conduct studies on microbial biofilms leading to improved strategies to diagnose, prevent and treat biofilm-associated infectious diseases. Collaborative projects, both domestic and international, that bring together investigators in diverse scientific disciplines studying biofilms, including microbiology, immunology (including mucosal immunology), biochemistry, clinical medicine, pathology, bioengineering, material science, imaging technology, and mathematical modeling are encouraged.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This Program Announcement, Research on Microbial Biofilms, is related to the priority areas of oral health, immunization and infectious diseases, unintentional injuries, diabetes and chronic disabling conditions, special population objectives, and heart disease and stroke. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report:

Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (Telephone: 202-512-1800). The document is also available on the at the following URL: http://odphp.osophs.dhhs.gov/pubs/hp2000/default.htm.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, including universities, colleges, hospitals, laboratories, units of State and local governments and eligible agencies of the Federal government. Collaborative projects with foreign scientists conducting unique research on microbial biofilms are encouraged. Also encouraged are applications that include investigators who are racial/ethnic minority individuals, women and persons with disabilities. Although an application must be submitted from a single institution, collaborative arrangements with other institutions are strongly encouraged.

MECHANISM OF SUPPORT

The mechanism of support utilized will be the individual research project grants (R01) and interactive or collaborative R01 grants. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this PA may not exceed five years. New investigators without prior R29 or R01 support are strongly encouraged to apply. Such applicants should identify themselves as first time applicants in a cover letter as well as in the application.

RESEARCH OBJECTIVES

Background

A biofilm is an accumulation of microorganisms (bacteria, fungi, and/or protozoa, with associated bacteriophages and other viruses) embedded in a polysaccharide matrix and adherent to solid biologic or non-biologic surface. Biofilms are medically important, accounting for over 80 percent of microbial infections in the body. Examples include infections of the: oral soft tissues, teeth and dental implants; middle ear; gastrointestinal tract; urogenital tract; airway/lung tissue, eye; urinary tract prostheses; peritoneal membrane and peritoneal dialysis catheters, indwelling catheters for hemodialysis and for chronic administration of chemotherapeutic agents (Hickman catheters); cardiac implants such as pacemakers, prosthetic heart valves, ventricular assist devices, and synthetic vascular grafts and stents; prostheses, internal fixation devices,

percutaneous sutures; and tracheal and ventilator tubing.

Several recent symposia and workshops sponsored by the American Society for Microbiology and the NIH have emphasized the unique features of bacteria and fungi growing as a biofilm rather than in free-floating, planktonic forms. In particular the microorganisms tend to be far more resistant to antimicrobial agents and to be particularly difficult for the host immune system to render an appropriate response.

The need for increased research on biofilms is based on many factors:

- Biofilms are remarkably difficult to treat with antimicrobials. The reasons for this are not clear. Antimicrobials may be readily inactivated or fail to penetrate into the biofilm. In addition, bacteria within biofilms have increased (up to 1000-fold higher) resistance to antimicrobial compounds, even though these same bacteria are sensitive to these agents if grown under planktonic conditions.

- Biofilms increase the opportunity for gene transfer between/among bacteria.
This is important since bacteria resistant to antimicrobials or chemical biocides can transfer the genes for resistance to neighboring susceptible bacteria. Gene transfer can convert a previous avirulent commensal organism into a highly virulent pathogen.

- Certain species of bacteria communicate with each other within the biofilm.
As their density increases, the organisms secrete low molecular weight molecules that signal when the population has reached a critical threshold. This process, called quorum sensing, is responsible for the expression of virulence factors. For example, Pseudomonas aeruginosa produces destructive proteinases when the number of these bacteria reach a high enough density in the airway biofilms of cystic fibrosis patients.

- Bacteria express new, and sometimes more virulent phenotypes when growing within a biofilm. Such phenotypes may not have been detected in the past because the organisms were grown on rich nutrient media under planktonic conditions. The growth conditions are quite different particularly in the depths of biofilms, where nutrients and oxygen are usually limited, and waste products from neighbors can be toxic. In short, bacteria found at the bottom of the biofilm look and act different than species located at the surface.

- Bacteria embedded within biofilms are resistant to both immunological and non-specific defense mechanisms of the body. Contact with a solid surface triggers the expression of a panel of

bacterial enzymes which catalyze the formation of sticky polysaccharides that promote colonization and protection. The structure of biofilms is such that immune responses may be directed only at those antigens found on the outer surface of the biofilm, and antibodies and other serum or salivary proteins often fail to penetrate into the biofilm. In addition, phagocytes are unable to effectively engulf a bacterium growing within a complex polysaccharide matrix attached to a solid surface. This causes the phagocyte to release large amounts of pro-inflammatory enzymes and cytokines, leading to inflammation and destruction of nearby tissues.

The field of biofilm research has traditionally been hindered by an inability to study the biofilm in non-destructive, three dimensional ways. In addition, it has been difficult or impossible to assess gene expression and metabolism of the microbe at the single cell level within a biofilm. However, as a result of advances in laser technology, digital imaging, scanning electron microscopy, and new fluorescent probes, researchers can now build a three dimensional model of biofilms and identify the location in the biofilm where specific genes are being expressed.

This broad-based initiative on microbial biofilms is designed to elucidate the mechanisms underlying their formation as well as development of strategies for the prevention and treatment of microbial biofilm-associated diseases. Moreover, this initiative is intended to capitalize on contemporary research in immunology, microbiology, bio-engineering and computer technology that might synergize with current biofilm research.

Research Objectives and Scope

Since microbial biofilms are a major problem affecting diverse anatomical locations of the body, several components of the NIH have joined in this Program Announcement. Examples of relevant research topics are listed below; however the list should not be construed as complete or restrictive. Applicants are encouraged to propose other topics that address the overall goal of this initiative which is to advance the understanding of the formation of biofilms, the means to control them, and their role in disease.

o Development of improved imaging of biofilms in situ;

o Development of improved clinically relevant in vitro and in vivo models of biofilms under specific in vivo conditions such as flow rate, nutrient content, and temperature;

o Development of better probes (genetic, metabolic, and immunological) for real-time analysis;

o Studies of quorum sensing/signaling molecules;

o Further characterization of biofilm-specific gene expression;

o Studies of the exchange of genetic material within biofilms;

o Studies of organic contaminants on substrata, and their influence on biofilm structure;

o Development of novel approaches to control pathogenic bacteria by, for example, devising strategies to favor growth of non-pathogenic microorganisms in biofilm communities;

o Studies of interactions of biofilms with host tissues and artificial implants;

o Development or use of novel agents, materials, or coatings for preventing or treating infections related to cardiovascular and pulmonary devices, and musculoskeletal prostheses (artificial joints), internal fixation devices, percutaneous sutures, and engineered tissues;

o Studies of pathogenic mechanisms of microbes growing in biofilms;

o Elucidation of mechanisms of resistance of biofilms to antimicrobial agents;

o Studies of host immune responses, both innate and adaptive to biofilms;

o Studies of the potential role of biofilms and host response in the development of systemic inflammatory response syndrome, septic shock, acute respiratory distress syndrome, and multiple organ dysfunction syndrome in injured or critically ill patients, or in model systems reflecting these clinical conditions;

o Studies of infectious lung disease in cystic fibrosis;

o Studies on the potential of diagnostic procedures such as bronchoalveolar lavage and bronchoscopy to disturb local biofilm flora and inoculate distant locations;

o Development of mathematical models and computer simulations of biofilms;

o Development of the methodology for the prevention and control of biofilms from catheters, water unit lines, and other clinically important solid surfaces; and,

o Sex, gender or age related issues involved in biofilm formation, prevention or treatment.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994, and is available at the following URL: http://grants.nih.gov/grants/guide/notice-files/not94-100.html

NIH POLICY AND GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL: http://www.nih.gov/grants/guide/notice-files/not98-024.html

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 5/95) is to be used in applying for these grants. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: grantsinfo@nih.gov. The forms are also available on the NIH Home Page at http://www.nih.gov/grants/funding/phs398/phs398.html

In order to identify the application as a response to this PA, the PA title (Research on Microbial Biofilms) and number PA-98-070 must be typed in item 2 of the face page of the application form and the YES box must be checked.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

Submit a signed, typewritten original of the application, including a cover letter, the checklist and five signed photocopies in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Review Procedures

Application will be assigned on the basis of established NIH referral guidelines. When the subject of an application is of interest to more than one Institute, dual assignments will be made. Upon receipt, applications will be reviewed for completeness by the Center for Scientific Review (CSR). Incomplete applications will be returned to the applicant without further consideration.

Applications that are complete will be evaluated for scientific and technical merit by study sections of the CSR. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

The five criteria to be used in the evaluation of grant applications are listed below. To put the criteria in context, the following information is provided to the peer reviewers.

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score and weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

Investigator: Is the investigator appropriately trained and well-suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

The initial review will also examine: the appropriateness of proposed budget and duration; the adequacy of plans to include children, genders, and minorities and their subgroups as appropriate for the scientific goals of the research and plans for the recruitment and retention of subjects; the

provisions for the protection of human and animal subjects; and the safety of the research environment.

AWARD CRITERIA

Meritorious applications received in response to this program announcement will compete for available funds with all other favorably recommended applications. Applicants should be aware that, in addition to scientific merit, program priorities and program balance, the total cost of the proposed project and the availability of funds will be considered by staff and the Advisory Council of the appropriate Institute in making funding recommendations. In this regard, since the costs associated with any new equipment needed to study biofilms, such as confocal scanning laser microscopes, microbalances, microprobes, and infrared spectrometers, can limit support for biofilm research, the establishment of collaborative arrangements with institutions that have these sophisticated resources is welcomed. In addition, the NIH values complementary funding from other public and private sources including foundations and industrial concerns. In circumstances when two or more applications have similar scientific merit, but vary in cost-competitiveness, the more cost-competitive application may be selected for funding.

INQUIRIES

Written, email, and telephone inquiries concerning this PA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Dennis F. Mangan, Ph.D.
Division of Extramural Research
National Institute of Dental Research
45 Center Drive, Room 4AN-32F, MSC 6402
Bethesda, MD 20892-6402
Telephone: (301) 594-2421
FAX: (301) 480-8318
Email: Dennis.Mangan@nih.gov

Stephen P. Heyse, M.D., M.P.H.
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases

Solar Building, Room 3A32
Bethesda, MD 20892
Telephone: (301) 496-7728
FAX: (301) 402-2508
Email: sh42i@nih.gov

Kenneth A. Gruber, Ph.D.
Division of Human Communication
National Institute on Deafness and Other Communication Disorders
6120 Executive Boulevard, Room 400C, MSC 7180
Bethesda, MD 20892-7180
Telephone: (301) 402-3458
FAX: (301) 402-6251
Email: Kenneth_Gruber@nih.gov

James S. Panagis, M.D., M.P.H.
Orthopaedics Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-37K, MSC 4500
Bethesda, MD 20892-6500
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: panagisj@ep.niams.nih.gov

Scott D. Somers, Ph.D.
Division of Pharmacology, Physiology, and Biological Chemistry
National Institute of General Medical Sciences
45 Center Drive, Room 2AS-49J, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5560
FAX: (301) 480-2802
Email: Somerss@NIGMS.NIH.GOV

Susan Banks-Schlegel, Ph.D.
Airway Biology and Disease Program
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, Room 10018, MSC 7952

Bethesda, MD 20892-7952
Telephone: (301) 435-0202
FAX: (301) 480-3557
Email: SchlegeS@gwgate.nhlbi.nih.gov

Lawrence Agodoa, M.D.
Division of Kidney, Urologic and Hematologic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
45 Center Drive, Room 6AS13B, MSC 6600
Bethesda, MD 20892-6600
Telephone: (301) 594-7717
FAX: (301) 480-3510
Email: AgodoaL@extra.niddk.nih.gov

Eugene G. Hayunga, Ph.D.
Research Policy Officer
Office of Research on Women's Health
National Institutes of Health
Building 1, Room 201
Bethesda, MD 20892
Telephone: (301) 402-1770
FAX: (301) 402-1798
Email: hayungae@od.nih.gov

Direct inquiries regarding grants management issues to:

Daniel Milstead
Division of Extramural Research
National Institute of Dental Research
45 Center Drive, Room 4AN-44A, MSC 6402
Bethesda, MD 20892-6402
Telephone: (301) 594-4800
FAX: (301) 480-8301
Email: Daniel.Milstead@nih.gov

Robert Tarwater
Grants Management Branch

National Institute of Allergy and Infectious Diseases
6003 Executive Boulevard, Room 4A29
Bethesda, MD 20892-7610
Telephone: (301) 496-7075
FAX: (301) 480-3780
Email: rt28o@nih.gov

Sharon Hunt
Division of Extramural Affairs
National Institute on Deafness and Other Communication Disorders
6120 Executive Boulevard, Room 400B, MSC 7180
Bethesda, MD 20892-7180
Telephone: (301) 402-0909
FAX: (301) 402-1758
Email: Sh79f@nih.gov

Vicki Maurer
Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-37H, MSC 4500
Bethesda, MD 20892-6500
Telephone: (301) 594-3504
FAX: (301) 480-5450
Email: maurerv@ep.niams.nih.gov

Toni Holland
Grants Management Office
National Institute of General Medical Sciences
45 Center Drive, Room 2AN-50B, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5132
FAX: (301) 480-3423
Email: Hollanda@NIGMS.NIH.GOV

Marie Willett
Grants Operations Branch
National Heart, Lung, and Blood Institute

Rockledge 2, Room 7156
Bethesda, MD 20892-7156
Telephone: (301) 435-0144
FAX: (301) 480-3310
Email: willettm@gwgate.nhlbi.nih.gov

Trude Hilliard
Division of Extramural Affairs
National Institute of Diabetes and Digestive and Kidney Diseases
45 Center Drive, Room 6AN-44B
Bethesda, MD 20892-6600
Telephone: (301) 594 8859
FAX: (301) 480 3504
Email: HilliardT@extra.niddk.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No.93.121 (NIDR), 93.856 (NIAID), and No. 93.173 (NIDCD), and No. 93.846 (NIAMS), No. 93.859 (NIGMS), No. 93.838 (NHLBI), and No. 93.849 (NIDDK). Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index
Return to NIH Guide Main Index